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# FREQUENCY DISTRIBUTION OF FOUR CYTOKINE GENE POLYMORPHISMS IN HEALTHY WESTERN KAZAKHSTAN POPULATION

**Abstract.** This study investigated a range of gene polymorphisms encoding IL-1, IL-6, IL-10, and TNF-α –308 in 100 healthy unrelated Kazakhs using real-time PCR. The findings were compared with published data on other populations. The distribution of genotypes was consistent with the Hardy−Weinberg equilibrium. However, the frequency of cytokine genotypes observed in the Kazakh population showed similarities and differences compared to neighboring ethnic groups. The most noticeable differences compared with Iranians, Turks, Russians, and Chinese were observed in the distribution of IL-1, IL-6, and IL-10 genotypes. The frequency of the TNF-α –308 genotype differed only with the Iranian population. Thus, our study showed a link between cytokine gene polymorphism and ethnicity. These results may be of clinical relevance in understanding the prevalence of diseases in Kazakhstan.

**Keywords:** allele frequencies, cytokines, gene polymorphism, population study, Kazakh population, Hardy−Weinberg equilibrium

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## РАСПРЕДЕЛЕНИЕ ЧАСТОТ ПОЛИМОРФИЗМОВ ЧЕТЫРЕХ ГЕНОВ ЦИТОКИНОВ В ЗДОРОВОЙ ПОПУЛЯЦИИ ЗАПАДНОГО КАЗАХСТАНА

**Аннотация.** Изучен ряд полиморфизмов генов, кодирующих IL-1, IL-6 и IL-10 и TNF-α –308, у 100 здоровых неродственных казахов с использованием ПЦР в реальном времени. Полученные результаты сравнивали с опубликованными данными по другим популяциям. Распределение генотипов соответствовало равновесию Харди–Вайнберга. Однако наблюдаемая частота генотипов цитокинов в казахской популяции показала сходство и различия по сравнению с соседними этническими группами. Наиболее заметные различия по сравнению с иранцами, турками, русскими и китайцами наблюдались в распределении генотипов IL-1, IL-6 и IL-10. Частота генотипа TNF-α –308 различалась только в иранской популяции. Таким образом, наше исследование показало связь между полиморфизмом генов цитокинов и этнической принадлежностью. Полученные нами результаты могут быть клинически значимы для понимания распространенности заболеваний в Казахстане.

**Ключевые слова:** частоты аллелей, цитокины, полиморфизм генов, популяционное исследование, казахская популяция, равновесие Харди–Вайнберга

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**Introduction.** Alleles and genotype frequencies are the main characteristics of a population. Each population contains a specific set of alleles of the different genes, and the range of genotype frequencies characterizes its gene pool. Thus, by studying the genetic composition of a population, it is possible to determine its immunogenetic profile and establish its specific features.

Cytokines constitute pleiotropic proteins involved in the pathogenesis of various multifactorial diseases [1]. Studies on cytokine gene polymorphisms that can lead to an imbalance in the inflammatory immune response are important in researching the body's response characteristics to internal and external stimuli [2]. For many polymorphic cytokine gene sites, the established inter-population differences

are not random but have ethnic patterns and may have been associated with human evolution [3]. Significant genetic differences in cytokine gene polymorphism distribution contributing to differences in disease incidence have been traced by ethnicity and geography [4]. Single nucleotide polymorphisms (SNPs) affect cytokine gene expression and susceptibility to diseases, disease progression, the severity of the clinical condition, and treatment results [5].

There were no reports on the studies that have reported allelic and genotypic diversity of cytokine genes interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α) among healthy Kazakh adults, compared with other populations. An international database of various cytokine polymorphisms is available on the Allele Frequency Net Database (URL: http://www.allelefrequencies.net/). However, as far as we know, this study is the first to report on the Kazakh population in relation to IL-1, IL-6, IL-10, and TNF-α –308 cytokine genes.

Kazakhstan is a sizable state in Eurasia, located between longitude 45 and 87° East, and latitude 40 and 55° North. Kazakhstan shares borders with Russia, China, Kyrgyzstan, Uzbekistan, and Turkmenistan. The inland Caspian Sea forms approximately half of its western boundary. Kazakhstan has no access to the ocean; it is the largest country in the world without this feature. At the beginning of 2020, its population consisted of various ethnic groups, such as Kazakhs (68.51 %), Russians (18.85 %), and Uzbeks (12.63 %) (Counties and their Cultures, Culture of Kazakhstan (URL: https://www.everyculture.com/Ja-Ma/Kazakhstan.html).

In this study, we analyzed the allelic and genotypic diversity of the cytokine genes IL-1β –511, IL-6 −174, IL-10 −1082, and TNF-α –308 among healthy Kazakh ethnic group adults, and their genetic relationships with various world populations to estimate the prevalence of allelic variants and genotypes of the promoter regions of the cytokine genes IL-1β –511 (rs16944), IL-6 −174 (rs1800795), IL-10 −1082 (rs1800896), and TNF-α –308 (rs1800629) in the healthy, adult Kazakhstan population. Additionally, we compared our results with published data for other populations.

**Materials and research methods.** *Subjects.* One hundred unrelated healthy Kazakh blood donors were randomly selected from Western Kazakhstan as the study subjects, using the knowledge and speaking of the native Kazakh language to identify the participants' ethnicity. The subjects filled out a questionnaire on nationality and were questioned on the history of marriages with other nationalities in their parents and grandparents. They confirmed that there were no marriages with other ethnic groups and that their native language was Kazakh. All volunteers were over 18 years (60 men and 40 women, mean age 44.7 ± 11.3 years) and received detailed information on the study. All subjects gave written informed consent before their blood samples were collected. They were genotyped for the polymorphism of four cytokine genes (IL-1β −511 C/T, IL-6 −174 G/C, IL-10 −1082 A/G, and TNF-α −308 G/A). The study was approved by the Institutional Review Board of the West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan, and conducted according to the 1964 Helsinki Declaration.

*Deoxyribonucleic acid (DNA) extraction and genotyping.* Genomic DNA isolation from peripheral blood leukocytes was performed using reagent kit DNA-Blood-M-100 (TestGen LLC, Russia). The method used by the kit is based on the reversible binding of nucleic acids on the surface of magnetic particles. The genotyping of the polymorphisms in the IL-1 (rs16944), IL-6 (rs1800795), IL-10 (rs1800896), TNF-α −308 G/A (rs1800629) gene was performed using thermal cycler for real time PCR DT-Prime M1 (DNA-technologies, Russia) and reagent kits for TaqMan SNP Genotyping Assays (TestGen, Russia). This method is based on real-time PCR to distinguish between two alleles of a particular SNP for use in genotyping studies. The TestGene reagent kits contained PCR primers and hybridization probes with terminal fluorescent dye (FAM) and fluorescence quencher (HEX) for each studied variant of genetic polymorphism (mutation). A round of temperature melting of the duplexes formed by the amplicons and signal probes was performed during the PCR, and the changes in fluorescence levels were recorded and graphically presented by the thermocycler software.

*Statistical analysis.* The allele and genotype frequencies were calculated by direct counting. Next, the observed and expected frequencies were compared using the $\chi^2$ test to check the Hardy−Weinberg equilibrium (HWE). The HWE hypothesis is rejected at the 5 % significance level ($p > 0.05$). The online HWE calculator (URL: https://wpcalc.com/en/equilibrium-hardy-weinberg/) was used for the calculation. Finally, the cytokine genotypic frequencies studied in the compared populations were assessed using the exact $\chi^2$ test. A two-tailed type I error of $p \leq 0.05$ at 95 % CI was assumed to be statistically sig-

nificant for all tests. All calculations were performed using the statistical software package Statistica 10.0 (Dell Technologies, Texas, USA).

**Research results.** The frequencies of alleles and genotypes in the Western Kazakhstan population are presented in Table 1. The distribution of frequencies in IL-1β –511, IL-6 −174, IL-10 −1082, and TNF-α –308 polymorphic genes did not significantly differ from the HWE, indicating a random distribution and lack of evolutionary forces acting in the formation of frequencies from these gene polymorphisms. The observed and expected frequencies were shown by the HWE ($p > 0.05$).

T a b l e 1. **Allele and genotype frequencies of four Kazakh population cytokine gene polymorphisms (*n* = 100)**

| Cytokine polymorphisms | Alleles/ genotypes observed | *N* | Genotype frequency | HWE *p*-value |
|---|---|---|---|---|
| IL-1β –511 | C | 118 (59.0) | 0.590 | |
| | T | 82 (41.0) | 0.410 | |
| | CC | 36 (36.0) | 0.360 | 0.886 |
| | CT | 46 (46.0) | 0.460 | |
| | TT | 18 (18.0) | 0.180 | |
| IL-6 –174 | C | 26 (13.0) | 0.130 | |
| | G | 174 (87.0) | 0.870 | |
| | CC | 3 (3.0) | 0.030 | 0.511 |
| | CG | 20 (20.0) | 0.200 | |
| | GG | 77 (77.0) | 0.770 | |
| IL-10 –1082 | A | 160 (80.0) | 0.800 | |
| | G | 40 (20.0) | 0.200 | |
| | AA | 64 (64.0) | 0.640 | 1.0 |
| | AG | 32 (32.0) | 0.320 | |
| | GG | 4 (4.0) | 0.040 | |
| TNF-α –308 | A | 17 (8.5) | 0.085 | |
| | G | 183 (91.5) | 0.915 | |
| | AA | 0 (0.0) | 0 | 0.650 |
| | AG | 17 (17.0) | 0.170 | |
| | GG | 83 (83.0) | 0.830 | |

N o t e. N – number of alleles (genotypes) observed; HWE – Hardy–Weinberg Equilibrium.

A comparison of the population ratios of cytokine alleles and genotype frequencies revealed significant differences between the Kazakh population data from this study and the data obtained for the Iranian [6, 7], Turkish [8, 9], Russian [10, 11], and Chinese [12, 13] ethnic groups (Table 2).

*IL-1β –511.* The CC genotype in the Kazakh population showed a significantly higher frequency than the Turks (36 % vs 22.9 %, $p = 0.039$) and Chinese (36 % vs 22.3 %, $p = 0.007$). The CT genotype in the Kazakh population was significantly lower than that of the Turks (46 % vs 62.9 %, $p = 0.015$), albeit higher than the Russians (46 % vs 33.6 %, $p = 0.032$).

*IL-6 −174.* The CC genotype in the Kazakh population showed a lower frequency than the Russians (3 % vs 23.2 %, $P < 0.001$) and a higher frequency than the Chinese (3 % vs 0 %, $p < 0.001$). The CG genotype in the Kazakh population was significantly lower than in the Iranian (20 % vs 68.7 %, $p < 0.001$) and the Russian populations (20 % vs 55 %, $p < 0.001$), but was significantly higher than in the Chinese population (20 % vs 1 %, $p < 0.001$). The GG genotype in Kazakhs showed a higher frequency than the Iranians (77 % vs 27.4 %, $p < 0.001$), Turks (77 % vs 63.9 %, $p = 0.039$), and Russians (77 % vs 21.8 %, $p < 0.001$); however, the frequency in the Chinese was higher (77 % vs 99 %, $p < 0.001$).

*IL-10 −1082.* The AA genotype in the Kazakh population showed a higher frequency than the Iranians (64 % vs 31.8 %, $p < 0.001$), Turks (64 % vs 37.8 %, $p < 0.001$), and Russians (64 % vs 16.8 %, $p < 0.001$), but was lower compared with the Chinese (64 % vs 89.3 %, $p < 0.001$). The GA genotype in the Kazakh population was significantly lower than in the Iranian (32 % vs 62.1 %, $p < 0.001$), Turkish (32 % vs 51.5 %, $p = 0.005$), and Russian populations (32 % vs 50 %, $p = 0.002$), but higher than in the Chinese population (32 % vs 9.7 %, $p < 0.001$). The GG genotype in Kazakhs showed a lower frequency than the Russians (4 % vs 33.2 %, $p < 0.001$) but higher than the Chinese (4 % vs 1 %, $p = 0.048$).

T a b l e 2. **Genotype frequencies of four Kazakh population cytokines compared with other populations, *n* (%)**

| Cytokine position genotypes | Kazakhs | Iranians[1, 2] | Turks[3, 4] | Russians[5, 6] | Chinese[7, 8] |
|---|---|---|---|---|---|
| IL-1β (–511): | *n* = 100 | [1]*n* = 312 | [3]*n* = 105 | [5]*n* = 238 | [7]*n* = 300 |
| CC | 36 (36.0) | 82 (26.3) | 24 (22.9)[a] | 100 (42.0) | 67 (22.3)[b] |
| CT | 46 (46.0) | 159 (51.0) | 66 (62.9)[c] | 80 (33.6)[d] | 163 (54.3) |
| TT | 18 (18.0) | 71 (22.7) | 15 (14.2) | 58 (24.4) | 70 (23.3) |
| IL-6 (–174): | *n* = 100 | [2]*n* = 261 | [4]*n* = 108 | [5]*n* = 238 | [8]*n* = 608 |
| CC | 3 (3.0) | 10 (3.9) | 5 (4.6) | 55 (23.2)[e] | 0 (0)[e] |
| CG | 20 (20.0) | 178 (68.7)[e] | 34 (31.5) | 131 (55.0)[e] | 6 (1.0)[e] |
| GG | 77 (77.0) | 71 (27.4)[e] | 69 (63.9)[f] | 52 (21.8)[e] | 599 (99.0)[e] |
| IL-10 (–1082): | *n* = 100 | [2]*n* = 261 | [3]*n* = 105 | [5]*n* = 238 | [7]*n* = 300 |
| AA | 64 (64.0) | 83 (31.8)[e] | 39 (37.8)[e] | 40 (16.8)[e] | 268 (89.3)[e] |
| GA | 32 (32.0) | 162 (62.1)[e] | 53 (51.5)[g] | 119 (50.0)[h] | 29 (9.7)[e] |
| GG | 4 (4.0) | 16 (6.1) | 11 (10.7) | 79 (33.2)[e] | 3 (1.0)[i] |
| TNF-α (–308): | *n* = 100 | [2]*n* = 261 | [3]*n* = 105 | [6]*n* = 217 | [8]*n* = 608 |
| AA | 0 (0.0) | 1 (0.4) | 1 (0.9) | 2 (0.9) | 3 (0.5) |
| AG | 17 (17.0) | 84 (33.0)[j] | 18 (17.1) | 40 (18.4) | 92 (15.2) |
| GG | 83 (83.0) | 170 (66.6)[k] | 86 (82.0) | 175 (80.6) | 510 (84.3) |

N o t e. Kazakh population: Kazakhs, $n = 100$ (our finding); 1 – Iranians, $n = 312$ (Khosravi et al., 2015); 2 – Iranians, $n = 261$ (Amirzargar et al., 2006); 3 – Turks, $n = 105$ (Çelik et al., 2006); 4 – Turks, $n = 108$ (Karaman et al., 2015); 5 – Russians, $n = 238$ (Samgina et al., 2017); 6 – Russians, $n = 217$ (Samgina et al., 2014); 7 – Chinese, $n = 300$ (Lu et al., 2005); 8 – Chinese, $n = 608$ (Wu et al., 2019). Differences in genotype and allele frequencies were compared using the $\chi^2$ test: a – $p = 0.039$; b – $p = 0.007$; c – $p = 0.015$; d – $p = 0.032$; e – $p < 0.001$; f – $p = 0.039$; g – $p = 0.005$; h – $p = 0.002$; i – $p = 0.048$; j – $p = 0.003$; k – $p = 0.002$.

*TNF-α −308*. The frequencies of alleles and genotypes in the Kazakh population significantly differed from the Iranian population only. The AP genotype in the Kazakh population showed a lower frequency than the Iranians (17 % vs 33 %, $p = 0.003$). Conversely, the GG genotype in the Kazakh population was significantly higher than in the Iranian population (83 % vs 66.6 %, $p = 0.002$). The distribution of allele and genotype frequencies in the Kazakh population was similar to the Turkish, Russian, and Chinese ethnic groups.

**Discussion.** Various cytokine gene polymorphisms associated with ethnic diversity can predispose a population to various diseases and can thus be used as a tool for anthropological research; these developments are important for improving the diagnosis, prognosis, and treatment of the disease [14]. This study was conducted in the Aktobe region of West Kazakhstan and is the first to describe the frequency of cytokine genotypes in the Kazakh population, demonstrating similarities and significant differences with the other populations. The results of cytokine gene polymorphisms and their association with ethnicity are presented in the literature [14, 15]. A comparison of the different population groups revealed similarities in cytokine genotypes and features of population distributions [16, 17]; however, there were no studies on the Kazakh population.

*Interleukin-1*, a central mediator of innate immunity and inflammation, is actively involved in the development of autoimmune, infectious, degenerative, and especially auto-inflammatory diseases. The interactions between bacterial agents, the environment, and genetic factors play an important role in the progression of tuberculosis. There is evidence that IL-1β may be associated with susceptibility to tuberculosis [12]. In 2019, the incidence of tuberculosis in Kazakhstan was 45.6 per 100,000 population (URL: https://pharm.reviews/images/document/sbornik-2019-compressed.pdf). This study determined the population distributions of IL-1 genotypes in Kazakhs compared to other population groups (Table 2). As mentioned, the CC genotype in the Kazakh population showed a higher frequency compared to the Turks and Chinese, while the CT genotype of the Kazakh population was significantly lower than that of the Turks. Genetically modified cytokine molecules affect the immune response. Therefore, studying the association of IL-1β gene polymorphism in tuberculosis patients within the Kazakh population may increase our knowledge for future studies on disease risks.

*Interleukin-6* is a multifunctional cytokine that mediates inflammatory and stress-induced reactions. There is strong evidence for associating IL-6 with the development of atherosclerotic cardiovascular

disease [18], which is the main cause of morbidity and mortality worldwide. In 2019, the incidence of coronary heart disease in Kazakhstan reached 554.8 per 100,000 population (URL: https://pharm.reviews/images/document/sbornik-2019-compressed.pdf). Our results showed that the CC genotype in the Kazakh population had a lower frequency than in the Russians and a higher frequency than in the Chinese (Table 2). The CG genotype in the Kazakh population was significantly lower than in the Iranian and Russian populations but higher than in the Chinese. The GG genotype in Kazakhs showed a higher frequency than in Iranians, Turks, and Russians, but a lower frequency than in the Chinese; therefore, IL-6 genetic profile analysis in the Kazakh population can elucidate specific features of coronary heart disease incidence in the Kazakh population.

*Interleukin-10* exhibits both immunosuppressive and antiangiogenic functions. A significant correlation exists between the IL-10 −1082 G/G genotype and an increased risk of breast cancer [19]. In 2019, the death rate from breast cancer in Kazakhstan was 6.1 per 100,000 female population (URL: https://pharm.reviews/images/document/sbornik-2019-compressed.pdf). According to our study, the AA genotype in the Kazakh population showed a higher frequency than the Iranians, Turks, and Russians but a lower frequency than the Chinese (Table 2). The GA genotype in the Kazakh population was significantly lower than in the Iranian, Turkish, and Russian populations but higher than in the Chinese population. Therefore, studying cytokine polymorphisms associated with the risk of breast cancer in the Kazakh population would be reasonable.

*TNF*-α is involved in systemic inflammation and primarily in the regulation of immune cells. In addition, TNF-α –308 G/A is involved in insulin resistance and is a candidate gene for type 2 diabetes susceptibility [20]. The incidence of diabetes mellitus in Kazakhstan in 2019 was 251.0 per 100,000 (URL: https://pharm.reviews/images/document/sbornik-2019-compressed.pdf). According to our data, the genotype frequencies in the Kazakh population significantly differed from the Iranian population only (Table 2). However, the distribution of genotype frequencies in the Kazakh population was the same as in the Turkish, Russian, and Chinese ethnic groups. Accordingly, it would be desirable to establish an association of TNF-α-308 gene polymorphism in patients with type 2 diabetes mellitus in the Kazakh population.

**Conclusion.** The data obtained are of interest for further studies on the association of cytokine gene polymorphisms with clinical course and possible outcomes of some topical multifactorial diseases. This study has demonstrated differences in the frequency distribution of some genotypes within the Kazakh population compared to other ethnic groups that might be clinically significant. However, the small number of participants was a major limitation; therefore, we cannot extrapolate the conclusions to the entire Kazakh ethnic group. Additionally, there was a lack of data on other cytokine polymorphisms. Therefore, larger studies are needed to confirm the initial findings and assess the significance of cytokine gene polymorphisms in predisposition to diseases to enhance our knowledge of the risk of different pathologies in the Kazakh population.

**Conflicts of interest.** The authors declare no conflict of interest.

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